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Single Center Experience of pulmonary thromboendarterectomy for Chronic Thromboembolic Pulmonary Hypertension: result from the TUMS-CTEPH registry

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Research Article

Keywords: pulmonary hypertension, Thromboendarterectomy, chronic thromboembolism

Posted Date: April 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1439519/v1

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Abstract

Introduction: Pulmonary thromboendarterectomy remains the preferred and potentially curative option for patients with chronic thromboembolic pulmonary hypertension (CTEPH). The objective of this study was to report the result of pulmonary thromboendarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH) in a single tertiary center.

Method: This study presents a analysis of CTEPH patients who underwent PEA enrolled in the Tabriz University of Medical sciences (TUMS-CTEPH) registry. This registry enrolled patients with CTEPH. The main outcome measures were Functional New York Heart Association [NYHA] class, 6-Minute Walk Distance, hemodynamic measures in right heart catheterization, morbidity and mortality.

Results: Here we reported 42 CTEPH patients who underwent PEA between January 2016 to October 2020. There were significant improvement in function class (2.6+-0.5 vs. 1.1+-0.34, p=0.00), mean PAP (47.1+-13 mmHg vs. post 27.9+-8 mmHg, p=0.000), cardiac output (4.3+-1.06 l/min vs. post 5.9+-1.2, p= 0.000), and pulmonary vascular resistance (709.4+-297.5 dynes • sec 1 • cm 5 vs. 214+-77 dynes • sec 1 • cm 5, p= 0.000). Fifteen patients (35%) developed complications. The most common complication was reperfusion injury in 10 (%23) patients. There was 4% post-surgical mortality during hospital admission and one year follow-up.

Conclusion: In this first single center report of PEA from Iran, post PEA and one year survival is comparable to that in other contemporary CTEPH centers. PEA can be performed safe with low mortality. Greater awareness of PEA and patients access to experienced CTEPH centers are important aim.

Introduction

The incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism is different among studies, but after acute PE, approximately 3.8% of patients go on to develop CTEPH (1). The main characteristics of CTEPH are intraluminal organizing thrombosis, fibrous stenosis of pulmonary artery and microvascular involvement and proliferation, resulting in pulmonary hypertension and progressive right heart failure (2).

In a long-term follow-up, high mean pulmonary artery pressure has been shown to be directly related to increased mortality. Mean pulmonary artery pressure (mPAP) > 50 mmhg resulted in a 2-year survival of less than 20% (3).

Medical therapy for the management of CTEPH increases mortality, and pulmonary thromboendarterectomy remains the preferred and potentially curative option for patients with CTEPH (3), with significant improvements in symptoms, pulmonary hemodynamics and survival. However, although surgery is a potentially curative treatment, only 0.9 endarterectomies per million are performed in the United States annually. The number of surgeries is higher in Europe, at approximately 1.7 per million (4), than in the United States. Among the surgical centers that perform pulmonary thromboendarterectomy,

the San Diego group has experience with more than 3000 pulmonary thromboendarterectomies since this group established thromboendarterectomy approximately 15 years ago (5,6).

Successful reports of surgery have been reported, mostly from the United States and Europe (7,8).

Recently, some centers in Asia (Japan) and Australia have reported successful results of surgery for CTEPH (9,10) patients with acceptable mortality.

The prospective follow up for understanding of outcome of patients with CTEPH (TUMBS-CTEPH) registry was designed to access the characteristics and outcomes of PEA in CTEPH patients in a specialized referral center in Tabriz-Iran. Aims of this study was to assess the patient characteristics, outcome of surgery and survival outcomes for patients with CTEPH enrolled in the TUMBS-CTEPH registry.

Methods

The present study was conducted from January 2016 to October 2020, and the protocol for the research and data collection was approved by the Ethics Committee of the University of Medical Sciences (approval number1399.592).

Patients data for the TUMS-CTEPH registry are collected directly from the electronic medical records, which are maintained on a disease-specific tool (PAH Tool; Inovultus Lda, Santa Maria da Feira, Portugal).

The data belonging to all patients with CTEPH in the mentioned period of time and those who had undergone pulmonary thromboendarterectomy (PEA) were examined.

A total of 97 patients were diagnosed with CTEPH, of whom 44 (45.3%) were male. All data, including epidemiological characteristics, the results of right cardiac catheterization, 6 Minute Walking Distance (6MWD), New York Hear Association (NYHA) Functional Class, perfusion scanning and surgical parameters and complications, were recorded. Parenchymal and mediastinal CT scans of all patients were examined by a radiologist, and the data related to mediastinal homeopathy and parenchymal evidence and signs related to CTEPH were recorded.

Of all the patients with CTEPH, 48 (49.1%) patients had a history of pulmonary embolism (PE), 12 (12.3%%) had DVT, 12 (12.3%) had pulmonary embolism and DVT, and 24 (24%) had no history of prior embolism or DVT.

Of all patients with CTEPH, 55 (56.7%) cases were inoperable due to the following reasons: Twenty-one (38%) patients had subsegmental and microvascular involvement and inconsistency between the results of hemodynamics and perfusion scanning, 8 (14.5%) had severe airway disease or other comorbidities, 5 (9%) had left heart diseases, 17 (30%) patients were unwilling to undergo surgery, and 4 (7%) was asymptomatic. In total, 42 patients underwent PTE.

In patients with CTEPH undergoing surgery, the mean pulmonary arterial pressure was 47.1+-13.2 mmHg, and the mean pulmonary vascular resistance (PVR) was 709.4+-297.5 dynes/s/cm [5]. Based on the New York and NYFC classification, 14 (33%) patients were classified as FCII, 25 (52%) FCIII, and 3 (7%) as FCIV.

The mean six-minute walk distance (6MWD) before surgery was 284+-120 m, with a reduction of 4% in O_2 saturation. Prior to the surgery, 3 (9%) patients had peripheral cyanosis, and 2 (6%) demonstrated bruit upon pulmonary auscultation. Patients were followed from the time of

enrollment until one year after PEA.

Right Heart Catheterization

All patients underwent right heart catheterization (RHC) before and after the surgery for a definite diagnosis, hemodynamic examination, and determination of PVR, mPAP, Co, and RA pressure.

A Swan-Ganz catheter was employed for all cases. RHC was performed, guided with ultrasound and through the internal jugular vein.

Resetting was performed for all patients at the mid-thoracic level. Cardiac output (Co) measurement was conducted using an Edwards device through the Fick and thermodilution methods. In 90% of cases, a blood sample was taken from the wedge point to ensure the catheter wedge. If wedge pressure could not be ensured, patients underwent left heart catheterization.

Anesthesia

Anesthesia was induced using ethomidate 0.2 mg/kg, midazolam 0.1 mg/kg, fentanyl 2–3 µg/kg and cisatracurium 0.2 mg/kg and was maintained intravenously using midazolam 100 µg/kg/h, fentanyl 5 µg/kg/h and cisatracurium 0.2 mg/kg/h. The patient's trachea was intubated as routine practice using a cuffed tube. After airway stabilization, a transesophageal probe was placed in the site, and we performed a basic survey. Then, using pressure wave form and transesophageal echocardiography, we placed central venous (8 f) and pulmonary arterial catheters, both from the right internal jugular vein. If there was any fresh thrombus on its passage, we advanced the catheter only to the superior vena cava. The pulmonary arterial catheter had the capability of continuously measuring cardiac output and mixed venous oxygen saturation (Edwards Lifesciences CCO Pulmonary Artery Catheter and Vigilance II monitor).

Continuous cerebral oximetry (INVOS™ system) was performed intraoperatively. We ran a cardiopulmonary bypass (CPB) at 27 C, keeping the activated clotting time > 500 sec and the Hct > 25 g/dl. During total circulatory arrest, the patient's temperature was decreased to 22 C.

Postoperative Period

Patients were mechanically ventilated in the intensive care unit (ICU) using synchronized intermittent mandatory ventilation with pressure support. The tidal volume was set as 6–8 mL/kg, with a positive endexpiratory pressure (PEEP) of 8 cm H2O and pressure support of 15 cm H2O above PEEP.

In the first 72 hours, the cardiac index was kept below 3 l/min. The patients were started on furosemide 2 mg/h for the first 24–72 hours, cefazolin (1 gr QID until extubation) and pantaprazol 40 mg IV. Heparin infusion was started as soon as possible and was changed to warfarin on the first postoperative day if no bleeding was present.

Statistical analysis

SPSS 13 statistical software (SPSS Inc., Chicago, IL) was used for the statistical analysis. Statistical significance was set at $P < 0.05$. The distributions of age, sex, echocardiographic variables (TAPSE, RAA, RVSP) and history of pulmonary embolism and deep vein thrombosis were measured using means and standard deviations for categorical variables.

Parametric paired tests were used to compare all variables, such as the means of the PVR, 6MWD, mean.PAP, function class and cardiac output, before and after surgery.

Results

In total, 42 patients underwent surgery, 21 (50%) of whom were women. The mean age of patients was 44 ± 14 years (21–67 years). Fourteen (33%) patients were FCII, 24 (57%) were FCIII, and 4 (9%) were FCIV.

Based on the San Diego lesion classification, 4 (9%) were at Level I, 20 (47%) at Level II, 14 (33%) at Level 3 and 4 (9%) at Level IV.

The mean duration of surgery was 6+-0.76 hours (7.5 to 4.5). Moreover, the total durations of circulatory arrest and cardiopulmonary bypass were 38+-18 minutes (69 to 10) and 137.6+-30 minutes (191 to 84 minutes), respectively. From among the 31 patients undergoing surgery, 13 (41%) required blood transfusion. The mean duration of using the Swan-Ganz catheter following surgery was 48 hours (24–72 hours).

Moreover, the mean duration of using mechanical ventilation equaled 70.2+-80.9 hours (6-287 hours).

The mean lengths of stay were 8.5+-5.9 days (2–27 days) in the ICU and 18.8+-10 days (10–35 days) in the hospital after surgery.

Overall, postoperative complications occurred in 15 (35%) patients. Three patients (7%) had bleeding, 10 (23%) had reperfusion injury, 7 (16%) had transient neurological complications, 2 (4%) had pneumothorax, and 6 (14%) had hemoptysis. Of patients with reperfusion injury, 9 (90%) experienced

improvement with pharmacotherapy, and VV ECMO was used for only 1 patient (10%). The duration of using ECMO in this patient was 72 hours. From among 42 patients undergoing surgery, intrahospital mortality occurred for 2 patient (4%) due to RV failure and reperfusion injury.

In the remaining 40 patients, the mean pulmonary arterial pressure was significantly reduced from 47.1 ± 13 mmHg preoperatively to 27.9 ± 8 mmHg postoperatively (p = 0.00). Furthermore, the PVR level was significantly improved, decreasing from 709.4 ± 297.5 dynes.Sec^{-1}.Cm^{-5} to 214 ± 77 dynes.Sec-1.Cm-5 (p = 0.000).

PVR showed no significant reduction in 1 patients (2.3%) and remained above 500 dynes.Sec^{-1}.Cm^{-5}, while decreasing to below 500 dynes.Sec^{-1}.Cm^{-5} in 39 (92%) patients.

Pulmonary vascular resistance was significantly higher in the patients with reperfusion injury (1029+-438 dynes.Sec^{-1}.$Cm^{-5)}$ compared to the patients without reperfusion injury (614.23+-338.17 dynes.Sec^{-1}.Cm^{-5} mmHg) (p = 0.003).

These two groups were also compared in terms of right atrial (RA) pressure, with no significant difference observed (12 ± 5 mmHg vs.10 ± 6 mmHg) (p = 0.48).

In the one-year postoperative follow-up, no patient had acute embolism or CTEPH relapse.

All patients were evaluated in terms of improvements in NYHA class, which showed that 33 (patients (82%) were FCI and 7 (17%) were FCII. Furthermore, the level of 6MWD indicated a significant improvement postoperatively (304 ± 113 m vs. 412 ± 98.8 m) (p = 0.002).

Discussion

Pulmonary thromboendarterectomy (PEA) is still the treatment of choice in patients with CTEPH. The expanded knowledge on PEA in the past few decades has resulted in a lower morality rate. The aims for performing thromboendarterectomy are to reduce PVR and to improve long-term performance (11).

Pulmonary thromboendarterectomy is associated with a higher chance of mortality than other routine cardiac operations and requires superior experience and skill (12,13). This study investigated the outcomes of 31 PEA cases in a medical center, with a high success rate and a low mortality rate. The first successful PEA was conducted by Ailison in 1960. Since then, more than 4,000 PEA operations have been performed across the world (14).

Among PEA centers, the University of California, San Diego, is the most prominent, with more than 3,000 surgeries and the lowest mortality rate (15). There are many published reports on its successful outcomes (15,16). The reported mortality rates in other centers vary between 5% and 24% depending on their previous experience (17,18).

This study showed that thromboendarterectomy drastically improved the patients' hemodynamics and performance. In this single-center experience, the overall postoperative mortality (5%) was lower than the mean operative mortality rate. After the surgery, PVR and the mean PAP were considerably reduced.

In 500 patients reported by the San Diego Center, 37.4% were type I, 49% were type II, 16% were type III, and 1.6% were type IV (15). In our study, 87% had proximal involvement, and only 22% had distal involvement.

One reason for the number of successful operations and the low mortality rate was the preoperative examination of the patients and their correct selection. Before surgery, the patients were examined for microvascular involvement, and those with PVR higher than 1000 dyn.s/cm^5 * were considered to be high-risk patients. This group was visited three times per day by the pulmonologist and the surgeon in the first five days after the surgery. In total, 27.5% of the patients had PVR higher than 1000 dyn.s/cm^5, out of which 7.2% experienced reperfusion injury. According to some studies, severe pulmonary hypertension (PH) increases postoperative mortality (19). A common dilemma is the use of pulmonary vasodilator as a preoperative bridging therapy. There are many studies exploring the use of these drugs in patients who cannot undergo surgery, (20,21) out of which only one randomized controlled trial (RCT) evaluating riociguat reported its positive effects through increasing 6MWD (22).

Although there is no multicenter RCT exploring the use of these drugs as bridging therapy and their role in reducing the mortality rate, a few single-blind studies on the effect of bosentan on 25 CTEPH patients showed a mortality rate of 31% among recipients of bosentan versus 25% among controls (23). The STEPH registry did not show a between-group difference in complications; however, the multivariate analysis showed that the bridging therapy was associated with an increased mortality rate. One reason could be the delay in referral for surgery and the changes made by these drugs on intra-arterial specimens. According to the results of these studies, none of the patients with high PVR received pulmonary vasodilators in our center, and the surgery was performed as soon as possible after referral.

In situ thrombosis is a common potentially fatal preoperative misdiagnosis of CTEPH in patients with idiopathic pulmonary arterial hypertension (IPAH), which is secondary to endothelial injury (24,25).

In 2015, a general evaluation and revision of postoperative care was conducted in our medical center based on the protocols of San Diego Center, including constant visits by a pulmonologist, maintaining a low cardiac index (CI) after the surgery, and establishing urination to reduce and control complications, specifically reperfusion injury, which resulted in significant reductions in mortality.

In this case series, high preoperative PVR was the leading cause of complications, specifically reperfusion injury, and morality; 1 patient died with a PVR higher than 1000 dyn.s/cm^5 and a mean PAP of 68 mmHg.

It is still uncertain whether other factors, such as high right arterial pressure, play a role in the development of such complications. The literature results showed a difference between patients with PVRs lower and higher than 1000 dyn.s/cm^5. Statistical data showed that hemodynamic disorders with

PVRs higher than 1000 dyn.s/cm^5 and mean PAPs higher than 50 mmHg were associated with high postoperative mortality (26). Some studies introduced aging as a risk factor for postoperative complications and mortality (27). In contrast, in our study, there was no relationship between aging and postoperative complications, and PVR was recognized as the most important risk factor. Moreover, some patients were mechanically ventilated for longer amounts of time. Regarding the lower pulmonary function of older patients, age can be a cause of longer ventilation after pulmonary operations, specifically reperfusion injury, which was not correlated with age. In general, RPI may occur in 10-40% of patients (28,29), with 60% of cases immediately after surgery, 30% in the first 48 hours after surgery (30), and sometimes 48 hours after surgery. In our study, RPI occurred within the first 24 hours after surgery. We tried to keep diuresis under mechanical ventilation (MV) and positive-end expiratory pressure (PEEP) and the CI was kept less than 3L/min/m2 with vasopressor.

A single-center study into the role of steroids in reducing RPI did not show any between-group differences (28). We did not use steroids to treat or prevent RPI in our patients. Studies have shown that avoiding inotropic and vasodilators and using a tidal volume of 8 mL/kg could reduce the chance of RPI (9). In case of a severe RPI and a postoperative increase in CI to >3 L/min/m^2, cardiac output reduction with vasopressors may lead to a reduction in capillary leakage and a reduction in RPI. We avoided prescribing inotropic drugs to reduce this complication and tried to keep the patient's CI lower than 3 using vasopressors.

If severe RPI does not respond to routine treatments, veno-venous ECMO (VV-ECMO) can be used. A case series published by the San Diego Center explained the use of ECMO for 20 out of 179 patients undergoing surgery over a period of 16 years (31). In this study, the survival rate was 30% in patients using EMCO versus 94.2% in patients did not receive it. The mortality rate in seven patients receiving ECMO within 120 hours after surgery was 100%. The latest global symposium on pulmonary hypertension recommended that this surgery should be performed in centers with appropriate equipment and conditions for ECMO placement (32).

Among our participants, only one patient needed VV-ECMO due to severe RPI and the lack of response to routine treatments. This patient developed severe reperfusion injury within 6 hours after surgery and received VV-ECMO due to the lack of response to supportive and pharmaceutical treatments within 24 hours. The ECMO was successfully removed from the patient after 72 hours. This patient stayed in the ICU and received MV for a longer time compared to other patients; in addition, the patient's preoperative PVR was approximately 1600 dynes.Sec^{-1}.Cm^{-5} and there was evidence of involvement in the proximal region and lobar artery. In the rest, RPI was managed through pharmacological and supportive treatments, and ECMO was not needed. Another postoperative complication of thromboendarterectomy in patients with CTEPH was persistent PH. There is no uniform definition for persistent PH after surgery, and its extent depends on the variable definition. In a study in England, approximately 30% of the patients showed high postoperative PH, based on MPAP>25 or PVR>240 dyn.s/cm^5 (33). However, their survival rate was 94%, and 82% of them were left untreated at Functional class I and II. Remained pulmonary hypertension and RV failure after thromboendarterectomy are the leading causes of early mortality.

In our study, the postoperative PH remained high in two patients (7%), which could be attributed to incomplete removal of the specimen in one case and microvascular involvement in the other, despite the successful operative outcome.

Bleeding is another probable complication after arterial thromboendarterectomy, which is generally due to either pericardial or airway bleeding. The reported extent of postoperative bleeding in the pericardium varies in different studies, ranging from 0.6 to 17% (34,35).

Pericardial bleeding may occur immediately after surgery or with a delay. In the first scenario, the patient is transferred to the operating room for bleeding control. In the second scenario, pericardial bleeding is controlled by temporary discontinuation of anticoagulants and drainage. Among our participants, two patients (8%) developed early postoperative pericardial bleeding and were transferred to the operating room for bleeding control.

However, management of airway bleeding due to arterial injury during surgery or RPI is a more complex problem. The first case is characterized by obvious and dark bleeding associated with the patient's pulse. The second case is characterized by diffuse and pink bleeding, with no need for further surgery. There was only one patient with no severe hemoptysis, who immediately underwent bronchoscopy, and the bleeding was controlled.

Conclusion

Pulmonary artery thromboembolism can be used safely, with a low mortality rate. Although extensive experience is needed for cases with distal involvement, pre- and postoperative team work is needed to improve the operative outcome. Anatomic involvement should be examined by CT angiography and perfusion scanning before surgery is decided upon.

Statements And Declarations

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript

Funding: *The authors declare that no funds, grants, or other support were received during the preparation of this manuscript*

Author contributions:

Dr. Farid Rashidi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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The first draft of the manuscript was written by Farid Rashidi, Rezayat Parvizi, and all authors commented on previous versions of the manuscript

All authors read and approved the final manuscript.

Conflict of Interest: None

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Tables

Table 1- Base line characteristics of the studied population

Total Number	97
Mean age	52.4+-16.3
Male gender	44 (45%)
History of PE[1]	48 (49.1)
History of DVT[2]	12 (12.3%)
History of DVT & PE	12 (12.3%)
Inoperable	55 (56.7%)
TRG [3] mmhg	65.5+-21
RVSP [4] mmhg	79.3+-24.2
IVC mm	21.8+-6.4
RAA [5]cm^2	22.6+-7.5
TAPSE [6]	17.3+-4.4

[1]PE= Pulmonary embolism [2]DVT= Deep vainthrombosis [2]TRG=Tricuspid regurgitation gradient [3] RVSP= Right ventricular systolic pressure [4] RAA= Right ventricular area [6] TAPSE= Tricuspid annular plane systolic excursion

Table 2- Demographic information of patients who underwent PEA

Total number	42
Mean age	44.5+-12.9
Male gender	21 (50%)
History of PE[1]	21 (50%)
Stay time in hospital/days	18.8+-10
Stay time in ICU/days	8.5+-5.9
Surgery time/hour	6+-0.76
Circulatory arrest time/min	38+-18
Cardiopulmonary bypass time	137.6+-30
Blood transfusion	13 (41%)
Mechanical ventilation time	70.2+-80.9

[1] PE=Pulmonary embilism

Table 3- The patient's variables at baseline and following pulmonary endarterectomy

Variable	Pre-PEA	Post-PEA	P value
NYHA Functional Class	2.6	1.1	0.00
6MWD (m)	304+-113	412+_98.8	0.002
Mean.PAP[1] (mmhg)	47.1+-13	27.9+-8	0.00
PVR[2] (dynes/s/cm[5])	709.4+-297.5	214+-77	0.00
Cardiac output/l/min	4.3+-1.06	5.9+-1.2	0.00

[1]PAP= Pulmonary artery pressure, [2] PVR=Pulmonary vascular resistance

Table 4- Complications after surgery

Complication	N	Percent
Mortality	2	4%
Reperfusion injury	10	23%
Hemoptysis	6	14%
Pericardial bleeding	3	7.1%
Respiratory failure require tracheostomy	0	0
Pneumothorax	2	4.2%
Transient neurologic	7	16.7%
ECHMO	1	2%